

Myeloperoxidase G-463A polymorphism and lung cancer: A HuGE Genetic Susceptibility to Environmental Carcinogens pooled analysis

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Myeloperoxidase is a phase I metabolic enzyme that converts the metabolites of benzo[a]pyrene from tobacco smoke into highly reactive epoxides. A polymorphism in the promoter region of myeloperoxidase (463G→A) has been found to be inversely associated with lung cancer; differences in the association with age and gender have been suggested. We conducted a pooled analysis of individual data from 10 studies (3688 cases and 3874 controls) from the Genetic Susceptibility to Environmental Carcinogens database. The odds ratio for lung cancer was 0.88 (95% confidence interval: 0.80–0.97) for the AG variant of myeloperoxidase G-463A polymorphism, and 0.71 (95% confidence interval: 0.57–0.88) for the AA variant after adjusting for smoking, age, gender, and ethnicity. The inverse association between lung cancer and myeloperoxidase G-463A polymorphism was equally found in males and females (odds ratio for the AA genotype 0.73 [95% confidence interval: 0.56–0.96] and 0.67 [95% confidence interval: 0.46–0.98], respectively), without differences in the association according to age in the two genders. The myeloperoxidase G-463A polymorphism was significantly protective in “ever” smokers but not in “never” smokers. Myeloperoxidase is a key enzyme in tobacco-induced carcinogenesis. *Genet Med* 2007;9(2):67–73.

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Myeloperoxidase (MPO) is the product of a single gene of approximately 11 kb composed of 11 introns and 12 exons, and located in the long arm of chromosome 17, segment q12–24.¹ The MPO protein is a tetramer composed of two 59-kD subunits, joined together by a single disulfide bridge containing a heme prosthetic group,² and two 12-kD subunits.³ MPO is synthesized as a large precursor polypeptide chain with a molecular weight of approximately 80 kD, is processed into the

enzymatically inactive apopro-MPO in the prelysosomal and lysosomal structures,⁴ and is then bound with the calcium-binding proteins calreticulin and calnexin in the endoplasmic reticulum. The insertion of a heme group converts the inactive form into the enzymatically active compound¹ found in large amounts in the azurophilic granules of polymorphonuclear neutrophils and in monocytes and macrophages.⁵ Three different MPO forms have been described,⁶ with similar spectral properties and amino acid composition but different substrate specificity and activity.

GENE FUNCTION

MPO is a phase I metabolic enzyme that converts lipophilic carcinogens into hydrophilic forms and activates several components of tobacco smoke, such as polycyclic aromatic amines and heterocyclic amines. MPO is also a component of the microbicidal network of polymorphonuclear leukocytes,^{3,7} which produces hypochlorous acid and other reactive oxygen species during the phagocytosis process.⁸ These oxidants can react with biological molecules to give secondary free radicals and have been associated with lipid peroxidation,⁹ DNA damage, single or double-strand breaks, denaturation or bases substitutions, DNA cross-linking,⁸ alterations in signal transduction pathways,¹⁰ and cell growth.¹¹

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Some 25% to 40% of the H_2O_2 produced by activated neutrophils may be converted to hypochlorous acid through reactions involving MPO,^{1,3,12,13} with subsequent extensive DNA base modification, including formation of chlorinated bases.¹⁴ The process is enhanced by the presence of tertiary amines, such as nicotine.¹⁵

GENE VARIANTS

Several single nucleotide polymorphisms have been identified in the MPO locus. The first reported polymorphism¹⁶ was a C→T substitution at nucleotide 8089 in exon 10; it causes hereditary MPO deficiency and affects 1 in 2000 to 4000 individuals. At the amino acid level, tryptophan (TGG) replaces arginine (CGG) at codon 569¹⁷ and results in a form of apoprotein MPO that does not undergo posttranslational processing to enzymatically active MPO species.¹⁸ Another polymorphism associated with MPO deficiency was identified in exon 4, corresponding to a -173Tyr→Cys change.¹⁹ The consequence is a modified MPO protein that remains in the endoplasmic reticulum bound to calreticulin and calnexin and then gets degraded. A further cause of MPO deficiency is a T→C transition causing the nonconservative replacement 251Met→Thr in the C-terminal region of the light chain and a 14-base pair deletion within exon 9.²⁰

A polymorphism located in the promoter region, 463 base pairs upstream of the MPO gene, decreases MPO gene expression by destroying a binding site for the SP1 transcription factor.²¹ The single G to A base substitution is associated with reduced MPO mRNA expression and decreased MPO enzyme levels,²⁰ whereas the G allele is associated with increased MPO production.¹ The base change leads to the loss of the SP1 transcription binding site in an *Alu* hormone-responsive element;²¹ these short DNA elements contain binding sites for key transcription factors, including retinoic acid receptor, estrogen receptor, PPARgamma, thyroid hormone receptor, and SP1 transcription factor.²² MPO activity in homozygous variant individuals (MPO-463AA) was reported to be more than three times lower than in homozygous wild-type subjects (MPO-463GG).²³ The MPO G/G genotype has been associated with acute promyelocytic leukemia,²⁴ coronary artery disease²⁵ and aerodigestive tract cancer,²⁶ early-onset multiple sclerosis,²⁷ increased incidence of Alzheimer disease,²⁸ and higher risk of periodontal disease in women, but not in men.²⁹ A recent meta-analysis³⁰ indicates that the variant alleles (GA plus AA) are associated with decreased risk of lung cancer in Japanese, and to a less extent in Caucasians.

DATA COLLECTION

The Genetic Susceptibility to Environmental Carcinogens (GSEC) database (<http://www.upci.upmc.edu/research/ccps/ccontrol/index.html>) is a collaborative project that gathers information from both published and unpublished case-control studies on metabolic gene polymorphisms and cancer.³¹ A

questionnaire was provided to each investigator at the time of enrollment in the study, collecting information on the study design, selection and source of controls, laboratory methods used for genotyping, source of DNA for genotype analysis, and response rates for both cases and controls. Studies reporting information on MPO G-463A and lung cancer were selected from the GSEC database. The investigators of the published studies for which data were not available through the GSEC project were then contacted and asked to provide their data for this specific pooled analysis. Of the 15 studies available from Medline, we obtained individual data from 10 studies for a total of 3688 cases and 3874 controls (Table 1).

Statistical analysis

The frequency of the MPO G-463A polymorphism in cases and controls was calculated, and the departure of MPO G-463A frequencies from expectation under Hardy-Weinberg (HW) equilibrium was tested among controls.³² Study-specific crude odds ratios (ORs) and 95% confidence intervals (CIs) for lung cancer were calculated. Summary ORs were calculated for all the studies combined; the Egger test was performed to assess publication bias³³ on the overall dataset and according to ethnicity when more than two studies were available (Caucasians, Asians, African Americans, and other ethnic groups). Funnel plots were used for a graphic representation of publication bias.

The Q statistic was used to test the hypothesis of homogeneity among all the studies, with *P* values less than .05 indicating the presence of heterogeneity among studies.³⁴ Adjusted ORs were then calculated using multivariate logistic regression models. Data were adjusted for ethnicity (Caucasians, Asians, African Americans, and others), age (as continuous variable and categorized as ≤50 and >50 years), study number, gender (male/female), and smoking status (never/ever).

The Armitage test for trend was used to assess the change in risk with smoking dose in subjects carrying the MPO polymorphism. All of the analyses were repeated excluding the studies in which the control frequencies were not in HW equilibrium.

GENOTYPE FREQUENCY

The frequency of the variant genotype AA of the MPO G-463A polymorphism was reported in a meta-analysis to be 5.4% in Caucasians,³⁰ slightly higher than what is reported in the GSEC database (4.6%, 95% CI 4.1–5.1), and 1.9% in Asians. The GSEC database shows higher frequencies of the AA variant in Asian populations (5.0%, 95% CI 4.3–6.1).

The frequency of the MPO G-463A polymorphism was 9.5% among the African American control populations included in the GSEC study and 5.2% in mixed populations (Table 2).

The distribution of the MPO G-463A polymorphism in the controls^{5,8,26,35,36,38,40,41,46,50,51,52} significantly departed from HW equilibrium in three of the studies included in the pooled analysis. The diverse ethnicity included in the study was the

Table 1

Studies included in the pooled analysis on myeloperoxidase and lung cancer: Genetic Susceptibility to Environmental Carcinogens dataset

Study reference no.	MPO	Cases	Controls	OR (95% CI)	Ethnicity	Source
5	GG	135 (55.6)	140 (57.1)	1.0 (ref)	Caucasian	Hospital
	GA	98 (40.3)	93 (38.0)	1.09 (0.76–1.58)		
	AA	10 (4.1)	12 (4.9)	0.86 (0.35–2.14)		
26	GG	141 (71.9)	185 (61.1) ^a	1.0 (ref)	Caucasian	Healthy
	GA	49 (25.0)	112 (37.0)	0.57 (0.37–0.90)		
	AA	6 (1.0)	6 (2.0)	1.31 (0.41–4.15)		
8,35,36	GG	235 (62.7)	202 (53.4)	1.0 (ref)	Caucasian	Healthy
	GA	126 (33.6)	157 (41.5)	0.69 (0.51–0.94)		
	AA	14 (3.7)	19 (5.0)	0.63 (0.29–1.36)		
38	GG	630 (65.5)	372 (66.2)	1.0 (ref)	Caucasian	Hospital
	GA	294 (30.6)	163 (29.0)	1.07 (0.87–1.31)		
	AA	38 (4.0)	27 (4.8)	0.83 (0.52–1.33)		
40	GG	190 (56.2)	398 (56.9) ^a	1.0 (ref)	Caucasian, A-A	Healthy
	GA	132 (39.1)	243 (34.7)	1.14 (0.85–1.53)		
	AA	16 (4.7)	59 (8.4)	0.57 (0.28–1.16)		
41	GG	234 (72.5)	294 (67.3) ^a	1.0 (ref)	Caucasian, Asian, other	Population
	GA	77 (23.8)	116 (26.5)	0.83 (0.58–1.19)		
	AA	12 (3.7)	27 (6.2)	0.56 (0.25–1.27)		
46	GG	76 (45.5)	71 (48.6)	1.0 (ref)	Caucasian, A-A, other	Healthy
	GA	79 (45.5)	68 (46.6)	1.09 (0.69–1.70)		
	AA	12 (7.2)	7 (4.8)	1.60 (0.68–3.80)		
50	GG	98 (65.3)	96 (55.8)	1.0 (ref)	Caucasian	Hospital
	GA	42 (28.0)	63 (36.3)	0.65 (0.39–1.09)		
	AA	10 (6.7)	13 (7.6)	0.75 (0.30–1.89)		
51	GG	193 (62.7)	181 (59.0)	1.0 (ref)	Caucasian, Asian, A-A, other	Hospital
	GA	106 (34.4)	111 (36.2)	0.90 (0.64–1.25)		
	AA	9 (2.9)	15 (4.9)	0.56 (0.22–1.45)		
52	GG	381 (60.9)	383 (61.4)	1.0 (ref)	Caucasian	Hospital
	GA	205 (32.7)	209 (33.5)	0.99 (0.78–1.25)		
	AA	40 (6.4)	32 (5.1)	1.26 (0.79–1.99)		

MPO, myeloperoxidase; CI, confidence interval; (ref) OR, odds ratio; A-A, African American.

^aSignificant departure from Hardy-Weinberg equilibrium.

reason for departure in two of the studies,^{40,41} and the reason was not known in one study.²⁶

SUMMARY OF THE PUBLISHED DATA

Before conducting the pooled analysis of individual data, we updated a previously published meta-analysis³⁰ by including information on 15 published studies comprising 5239 cases and 5066 controls. The summary estimate for the association between the MPO variant (AG plus GG) and lung cancer was 0.91 (95% CI: 0.84–0.99) using a random effect model because of the significant heterogeneity among studies (Q test =

31.477, $P = .005$). There was no evidence of publication bias (P value was .1 for the Egger's test and .2 for the Begg test).

POOLED ANALYSIS

Overall, there was a significant inverse association between the MPO G-463A polymorphism and lung cancer, with a significant trend (Table 2). The OR was 0.88 (95% CI: 0.80–0.97) for the AG variant of MPO G-463A polymorphism and 0.71 (95% CI: 0.57–0.88) for the AA variant. There was some evidence of heterogeneity among studies for the association between the heterozygous variant MPO and lung cancer. A sen-

Table 2

Association between myeloperoxidase polymorphism and lung cancer according to ethnicity, gender, and smoking status

	MPO	Cases	Controls	OR (95% CI)	
Caucasians (10 studies) ^a	GG	2072 (63.2)	1952 (59.6)	1.0 (ref)	
	GA	1061 (32.4)	1144 (35.0)	0.86 (0.78–0.96)	
	AA	145 (4.4)	177 (5.4)	0.73 (0.58–0.93)	
African-Americans (3 studies) ^a	GG	87 (42.4)	131 (50.0)	1.0 (ref)	
	GA	101 (49.3)	106 (40.5)	1.37 (0.91–2.07)	
	AA	17 (8.3)	25 (9.5)	0.79 (0.39–1.61)	
Asians (2 studies) ^a	GG	84 (77.8)	115 (70.6)	1.0 (ref)	
	GA	23 (21.3)	41 (25.1)	0.83 (0.45–1.53)	
	AA	1 (0.9)	7 (4.3)	0.19 (0.02–1.65)	
Others (3 studies) ^a	GG	69 (72.6)	86 (74.8)	1.0 (ref)	
	GA	22 (23.2)	23 (20.0)	1.10 (0.53–2.28)	
	AA	4 (4.2)	6 (5.2)	0.96 (0.23–4.05)	
Males ^b	GG	1600 (63.5)	1554 (59.5)	1.0 (ref)	
	GA	806 (32.0)	917 (35.1)	0.84 (0.74–0.95)	
	AA	114 (4.5)	141 (5.4)	0.73 (0.56–0.96)	
Females ^b	GG	713 (61.1)	768 (60.9)	1.0 (ref)	
	GA	402 (34.4)	418 (32.1)	0.99 (0.84–1.19)	
	AA	53 (4.5)	76 (6.0)	0.67 (0.46–0.98)	
Never smokers ^c	GG	179 (64.0)	529 (64.1)	1.0 (ref)	
	GA	88 (31.4)	246 (29.8)	0.89 (0.65–1.21)	
	AA	13 (4.6)	50 (6.1)	0.76 (0.39–1.47)	
Ever smokers ^c	GG	2079 (62.7)	1587 (58.6)	1.0 (ref)	
	GA	1087 (32.8)	961 (35.5)	0.88 (0.79–0.98)	
	AA	148 (4.5)	161 (5.9)	0.72 (0.57–0.91)	
Overall	GG	2313 (62.7)	2322 (59.9)	1.0 (ref) ^d	1.0 (ref) ^e
	GA	1208 (32.8)	1335 (34.5)	0.94 (0.86–1.0) ^e	0.88 (0.80–0.97)
	AA	167 (4.5)	217 (5.6)	0.87 (0.69–1.08) ^{f,h}	0.71 (0.57–0.88)

MPO, myeloperoxidase; (ref) OR, odds ratio; CI, confidence interval.

^aAdjusted for smoking status (never/ever), age (≤ 50 and > 50 years), study number, and gender.^bAdjusted for smoking status (never/ever), age (≤ 50 and > 50 years), study number, and race.^cAdjusted for age (≤ 50 and > 50 years), study number, gender, and race.^dRandom effect model.^e*P* value Q test: .07, *P* value Egger's test: .06.^f*P* value Q test: .44, *P* value Egger's test: .45.^gAdjusted for race, smoking status (never/ever), age (≤ 50 and > 50 years), study number, and gender.^hTest for trend: 8.2, *P* < .05.

sitivity analysis suggested that the heterogeneity was deriving from the different ethnicities included in the studies. The stratified analysis according to ethnicity confirms the inverse association in Caucasians; the same trend, although nonsignificant, was observed in Asian and African-American populations. No association was observed in the group including mixed ethnicity. The inverse association between lung cancer and MPO G-463A polymorphism was equally found in males and females (OR for the AA genotype 0.73 [95% CI: 0.56–0.96] and 0.67 [95% CI: 0.46–0.98], respectively), without differences in the association according to age in the two genders (data not shown).

The MPO G-463A polymorphism was significantly inversely associated with lung cancer in ever smokers but not in never smokers; the OR for lung cancer with the AA homozygous MPO variant was 0.76 (95% CI: 0.39–1.47) in never smokers and 0.72 (95% CI: 0.57–0.91) among ever smokers. However, a statistical interaction between smoking and the MPO polymorphism was not observed.

Among smokers, an increased risk of lung cancer was observed with increasing smoking dose in subjects carrying the GG wild-type genotype to a greater extent than for the GA and AA genotypes (Table 3). A significant trend for the decrease in

Table 3

Association between smoking intensity and lung cancer according to myeloperoxidase genotype

Smoking status	GG OR (95% CI) (n cases/n controls)	GA OR (95% CI) (n cases/n controls)	AA OR (95% CI) (n cases/n controls)
Never smokers	1.0 (ref) (179/529)	1.0 (ref) (88/246)	1.0 (ref) (13/50)
≤10 cigarettes/d	1.96 (1.49–2.56) (148/235)	2.02 (1.41–2.87) 103/155	1.54 (0.62–3.83) 12/31
11–20 cigarettes/d	3.15 (2.52–3.93) (456/501)	2.74 (2.01–3.73) 245/296	2.53 (1.18–5.41) 38/59
>20 cigarettes/d	3.98 (3.19–4.96) (590/525)	3.36 (2.47–4.56) 321/337	3.05 (1.39–6.70) ^a 36/47
<50 pack-y	2.56 (2.08–3.15) (1139/996)	2.22 (1.66–2.96) (604/620)	2.14 (1.04–4.38) ^b (91/110)
>50 pack-y	4.55 (3.64–5.68) (880/544)	4.10 (3.01–5.58) (453/317)	4.08 (1.85–9.01) ^b (56/44)

(ref) OR, odds ratio; CI, confidence interval.

Data are adjusted for age, study number, race, and gender.

Armitage test for trend across MPO genotype categories: ^a*P* < .05; ^b*P* < .01.

the association between smoking and lung cancer according to the MPO polymorphism was observed among smokers of 20 or more cigarettes per day. A similar phenomenon was observed when looking at pack-years as a measure of smoking history (Table 3). No changes in the association between occupational exposure and lung cancer according to the MPO G-463A polymorphism were observed (data not shown).

The association between the MPO G-463A polymorphism and lung cancer varied little according to histologic types (Table 4), with a slightly more protective effect present in carcinoma non otherwise specified than in other subtypes.

DISCUSSION

This pooled analysis of 10 published studies including 3688 cases and 3874 controls confirms the inverse relationship between lung cancer and the MPO G-463A polymorphism reported by a previous meta-analysis.³⁰ In addition, we stratified the data according to ethnicity and observed that the association was present in Caucasians and was suggested in Asians but did not seem to be confirmed in populations of African or mixed descents, although the sample size of the latter group was limited in our study. Pooling of individual data has several advantages on a meta-analysis of published data, as described elsewhere.⁵³ Because the pooled dataset includes additional information on several cofactors, it is possible to adjust the point estimates for potential confounding factors, to perform strati-

fied analyses, and to study possible sources of heterogeneity. The present analysis assessed the pooled risk of lung cancer separately for both the MPO GA and the GG polymorphism, something that could not be done with a simple meta-analysis because of the restriction imposed by the availability of aggregate data from published studies. In addition, we stratified the data by ethnicity, gender, and age groups, another task that could not be fulfilled with a meta-analysis.

The MPO G-463A polymorphism displayed a significant inverse association with lung cancer in smokers, and in this group the effect was more marked with increasing smoking dose. A study in white smokers showed that DNA adduct levels in MPO-AA individuals were twofold lower than in MPO-AG subjects and fivefold lower than in MPO-GG subjects; MPO activity in homozygous variant individuals (MPO-463AA) was more than three times lower than in homozygous wild-type subjects (MPO-463GG).²³

The association between MPO G-463A and lung cancer restricted to current smokers was suggested by a previous study.³⁵ More recent studies reported an interaction with smoking and smoking dose,^{8,36–39} which was not confirmed by our analysis, although the association between smoking and lung cancer weakens in subjects carrying the heterozygous MPO variant, and even more in subjects carrying the homozygous variant form of the gene. It is likely that the reduced enzymatic activity of the MPO variant reduces the amount of

Table 4

Association between myeloperoxidase polymorphism and lung cancer according to histologic type

Histology	MPO GG N (%)	MPO GA, AA N (%)	OR ^a (95% CI)
Adenocarcinoma	689 (62.3)	417 (37.7)	0.84 (0.73–0.98)
Squamous cell carcinoma	624 (61.6)	389 (38.4)	0.84 (0.72–0.99)
Small cell	356 (65.9)	184 (34.1)	0.75 (0.61–0.92)
Large cell	62 (64.6)	34 (35.4)	0.72 (0.47–1.13)
Mixed	201 (58.1)	145 (41.9)	1.04 (0.82–1.31)
Carcinoma not specified	110 (70.5)	46 (29.5)	0.63 (0.44–0.91)

MPO, myeloperoxidase; OR, odds ratio; CI, confidence interval.

^aOR of GA or AA versus GG adjusted for race, smoking status (never/ever), age (≤50 and >50 years), study number, and gender.

available carcinogens produced as by-products of the metabolism of tobacco constituents.

The association of the MPO G-463A polymorphism by lung cancer histologic types has been conflicting, probably because of the small size of previous subgroup analyses. Nine published studies report information on histology, five of them with negative results,^{5,40–43} one with a more pronounced protective effect in squamous cell carcinoma,³⁷ one with a more pronounced effect in adenocarcinoma,²⁶ and two with a more pronounced effect in small cell carcinoma.^{36,44} In the present pooled analysis, the association between the MPO G-463A polymorphism and lung cancer did not vary significantly according to histologic type, with perhaps a more evident inverse association for carcinoma not otherwise specified.

Previous studies^{8,35,36,39,45} indicated an inverse association between MPO and lung cancer in men, whereas others did not confirm the result.^{26,41,43,46} Although we did not observe statistically significant differences with gender, the protective effect of the A allele seemed to be more pronounced in males than in females, after adjustment for several confounding factors. It has been indicated⁴⁷ that the A allele is associated with the creation of an estrogen receptor binding site and with higher inducible levels of MPO by estrogen. In vitro studies suggest that estrogens increase the MPO A allele promoter activity by several fold; females carrying at least one MPO A allele have been reported as having significantly higher levels of DNA adducts than those carrying the MPO G/G genotype.⁴⁸

Another published finding is that the MPO G-463A polymorphism may be more protective toward lung cancer in younger individuals,^{8,35,36,39,45} although other studies did not confirm this observation^{26,40,43,46} or reported the opposite.^{38,44} MPO activity has been reported to be lower in women with the -463GA genotype who are aged less than 45 years than in those aged more than 55 years with the same genotype.⁴⁹ The opposite effect, although not significant, was found in men.⁴⁹ We did not observe differences in the association according to age in the two genders. Most individual studies will not have large numbers of young subjects; therefore, the reported age modification effects are likely to be derived from the small sample size of previous studies.

CONCLUSION

The large dataset deriving from the GSEC study and the ability to adjust the data for confounding factors gave us the opportunity to contribute to the understanding of the role played by gender, age, and smoking habits in the association between MPO and lung cancer. It is possible that gender and age differences in lung cancer risk related to the MPO G-463A polymorphism actually reflect gender and age differences in length or duration of smoking, two cofactors that may not have always been controlled for in the analysis.

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